correcting the aberrant expression/phosphorylation of bone mineral matrix proteins (osteopontin/osteocalcin). The RGD cell attachment sequence and also the glycosaminoglycan attachment motif could be required for the functional nucleation and crystallization of hydroxyapatite and bone mineral.

Growth impairment is a major feature of HYP, and current treatments are unsuitable. Treatment by administration of phosphatonin-derived fragments as opposed to inorganic phosphate and vitamin D supplementation, may correct this.

Accordingly, among the useful effects of peptide fragments of phosphatonin are:

1. Correction of hypophosphatemia (NaPi, preferably renal)
2. Normalization of 24-hydroxylase 1 alpha hydroxylase activity (renal).
3. mineralization of bone and bone repair (correction/prevention of rickets).
4. Complete loss of bone pain symptoms.
5. Correction of stunted growth.

Oncogenic hypophosphatemic osteomalacia (OHO):

The clinical profile of OHO is similar to HYP. There is a renal phosphate leak, low circulating levels of 1,25 dihydroxy vitamin D3 (calcitriol), elevated alkaline phosphatase, bone hypomineralization that in adults is presented as a generalized bone softening (osteomalacia) and low serum phosphate. The pathophysiologies of HYP and OHO clearly overlap. In rickets, the defect is a non functional PHEX gene. However, in OHO it is circulating unprocessed phosphatonin. The tumours are often difficult to find, and can be extremely difficult and dangerous to resect. Control of phosphate metabolism and bone mineralization is essential when removal of tumour is contra-indicated. Administration of PHEX to patients to cleave hormone is predicted to be dangerous as other circulating hormones and proteins may also be affected by promiscuous cleavage. Phosphatonin-fragments could instead be designed that have high receptor affinity and bioactivity, such that they would compete effectively with unprocessed tumour-derived circulating hormone.

Other rickets or hypophosphatemic conditions:

There are many causes of rickets besides HYP and OHO, the most common involve abnormalities of vitamin D, but there are causes such as hypophosphatemia, renal tubular acidosis, use of certain medications, sprue, cystic fibrosis etc. Use of fragments of phosphatonin, and phosphatonin itself may be of use in treating these diseases. Some of the diseases are briefly discussed below (diseases resulting in hyperphosphatemia are potentially treatable by use of the whole hormone).

- Renal transplants and renal osteodystrophy:

  A chronic feature of renal transplantation is the development of a renal phosphate leak (hypophosphatemia), and abnormal bone mineralization. Phosphatonin fragments would be effective in treating this without the side-effects associated with current medications.

  Osteodystophy (a combination of bone disorders), is usually caused by chronic kidney failure (renal disease). Renal failure will result in death, unless dialysis is given (end stage renal disease). Therefore, patients with osteodystrophy are usually on dialysis therapy. This bone disease, which is also referred to as "renal osteodystrophy", is common in patients on chronic hemodialysis. Secondary hyperparathyroidism develops in most patients with chronic renal failure, and is associated with the histologic finding of osteitis fibrosa cystica. The disease is characterized by growth failure and severe bone deformities in children, especially the very young. The pathogenesis of renal osteodystrophy is related to phosphate retention (hyperphosphatemia), and its effect on calcium and calcitriol metabolism, in addition to roles played by metabolic acidosis, cytokines, and degradation of parathyroid hormone. Treatment includes restriction of dietary phosphorous intake, phosphate binders, and use of active metabolites of vitamin D. In this context addition of unprocessed hormone would be a powerful means of controlling phosphate levels, and would lead to bone healing. If receptors for phosphatonin are expressed in a range of tissues as well as the kidney, then the potential for treating patients with end stage renal disease exists (i.e. complete loss of kidney function).

- Osteoporosis/bone mineral loss:
  Post-menopausal women are prone to loss of bone mineral with consequent damage to the integrity of the skeleton. The cause is unknown but is likely to involve a complex interaction of genetic and environmental factors. Current research is focussed on refining statistical models to analyze multifactorial diseases such as osteoporosis.

  The use of phosphatonin-derivative fragment(s) would help in the treatment of this disease by potentially reversing the bone mineral loss. Moreover, the bioactive peptides could be modified to increase potency and specificity of action.

- Pagets disease of bone:
  Pagets disease occurs due to asynchronous bone re-modeling. Bone mineralization (mediated by osteoblasts), and bone resorption (mediated by osteoclasts), are out of step. Excessive osteoclast resorptive activity occurs (predominantly in the early resorptive phase), and bone marrow is replaced by fibrous tissue and disorganized trabeculae. Although the cause is unknown, administration of peptide derivatives of phosphatonin may help in the treatment of the disease.

- Diseases related to disorders in NaPi in other tissues than kidney:
  The sodium dependent phosphate co-transporter (NaPi) is expressed not just in the kidney but in many other tissues. Three type of NaPi, namely Type I, II, and III have been described thus far and all of them are said to be expressed in the kidney. In tissues other than the kidney, Type III is said to be expressed ubiquitously (Murer, Eur. J. Physiol. 433 (1997) 379-389; Kavanaugh, Kidney Int. 49 (1996) 956-963) and Type I has been confirmed to be expressed in the liver and brain in addition to the kidney (Hilfiker, PNAS 95 (1998), 14564-14569). On the other hand, Type II had been believed to be expressed only in the proximal tubule of the kidney.